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TITLE: Method for antibody targeting of therapeutic agents

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INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hansen; Hans John	Westfield	NJ		

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CLAIMS:

What is claimed is:

1. A method for targeting a cytotoxic agent to a target site, comprising the steps of:

(a) injecting a mammal parenterally with an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope on an enzyme, wherein binding to said epitope does not interfere with enzyme activity;

(b) subsequently injecting said mammal parenterally with an effective amount for enzyme activity of said enzyme, such that said bispecific antibody or antibody fragment binds said enzyme to form an antibody-enzyme conjugate in situ; and

(c) after a sufficient period of time for localization of said antibody-enzyme conjugate at the target site and for unbound antibody-enzyme conjugate to clear from the circulatory system of the mammal, further injecting said mammal parenterally with an effective amount for deposition at said site of a serum soluble polymer substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising a cytotoxic agent that is relatively insoluble in serum in vivo, wherein the cytotoxic agent partitions out once the substrate-agent conjugate is acted upon by the enzyme component of the targeted antibody-enzyme conjugate, so that the agent then accretes at the target site to a significantly greater extent than the substrate-agent conjugate would accrete in the absence of the enzyme, said polymer substrate-agent conjugate comprising a polymer substrate for said enzyme, wherein either (1) a plurality of molecules of said agent are linked to said polymer substrate, or (2) said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent;

wherein said enzyme is selected from the group consisting of dextranase, cellulase and beta-glucosidase.

2. The method of claim 1, wherein in step (b), said enzyme is injected after a sufficient time for said bispecific antibody or antibody fragment to localize at said site and for unbound bispecific antibody or antibody fragment to substantially clear from the circulation of said mammal.

3. The method of claim 1, wherein said antibody or antibody fragment in said antibody-enzyme conjugate specifically binds to an antigen produced by or associated with a member selected from the group consisting of a tumor, an infectious lesion, a parasitic lesion, a fibrin clot, a myocardial infarction, an atherosclerotic plaque, a non-cancerous cell that has an antigen that enables targeting of said non-cancerous cell by said antibody-enzyme conjugate and a damage-related site of a damaged, non-cancerous cell.

4. The method of claim 1, wherein said enzyme is a dextranase or a cellulase, and wherein said polymer substrate-agent conjugate comprises said agent conjugated to (1) at least one solubilizing dextran or carboxymethylcellulose oligomer which is a polymer substrate for said enzyme and (2) a non-substrate aminodextran or a polylysine carrier.

5. The method of claim 1, wherein said mammal is a human.

6. A sterile injectable preparation, for targeting a cytotoxic agent to a target site, comprising;

(a) a first sterile injectable solution containing an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope of an enzyme, wherein binding to said epitope does not interfere with enzyme activity, said antibody or antibody fragment being dissolved in a pharmaceutically acceptable sterile injection vehicle;

(b) a second sterile injectable solution containing an effective amount for enzyme activity at said target site of said enzyme, said enzyme being dissolved in a pharmaceutically acceptable sterile injection vehicle; and

(c) a third sterile injectable solution containing an effective amount, for deposition at said site, of a serum soluble polymer substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising at least one cytotoxic agent that is relatively insoluble in serum in vivo, said polymer substrate-agent conjugate comprising a polymer substrate for said enzyme, wherein either (1) a plurality of molecules of said agent are linked to said polymer substrate, or (2) said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent, said polymer substrate-agent conjugate being dissolved in a pharmaceutically acceptable sterile injection vehicle;

wherein said enzyme is selected from the group consisting of dextranase, cellulase, and beta-glucosidase.

7. A kit, for targeting a cytotoxic agent to a target site, comprising;

(a) a first sterile container containing an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope of an enzyme which does not interfere with enzyme activity;

(b) a second sterile container containing an effective amount for enzyme activity at said target site of said enzyme; and

(c) a third sterile container containing an effective amount for deposition at said site of a serum soluble polymer substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising a cytotoxic agent that is relatively insoluble in serum in vivo, said polymer substrate-agent conjugate comprising a polymer substrate for said enzyme, wherein either (1) a plurality of molecules of said agent are linked to said polymer substrate, or (2) said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent;

wherein said enzyme is selected from the group consisting of dextranase, cellulase, and beta-glucosidase.

8. A method as claimed in claim 1, wherein said polymer substrate is a dextran and said enzyme is dextranase.

9. A method as claimed in claim 1, wherein said polymer substrate is aminodextran and said enzyme is dextranase.

10. A method as claimed in claim 9, wherein said agent is linked to amino groups of said aminodextran.

11. A method as claimed in claim 10, wherein said cytotoxic agent is a drug that is loaded onto said amino dextran in a ratio of monosaccharide subunits to drug of from about 3 to about 25.

12. The method as claimed in claim 1, wherein said polymer substrate is a carboxymethylcellulose which comprises functional groups to which said cytotoxic agent is linked and wherein said enzyme is cellulase.

13. A method as claimed in claim 9, wherein said agent is linked to functional groups of a carboxymethylcellulose.

14. A method as claimed in claim 1, wherein said polymer substrate-agent conjugate comprises a cytotoxic agent, wherein the cytotoxicity of cytotoxic agent is reduced by conversion to a conjugate with said polymer substrate.

15. A method as claimed in claim 1, wherein said plurality of molecules of said agent are linked to the backbone of said polymer substrate.

16. A method as claimed in claim 1, wherein said plurality of molecules of said agent are linked to oligomers that are substrates for the enzyme, and said oligomers are linked to the backbone of a polymer substrate.

17. A method as claimed in claim 1, wherein said polymer substrate is a coating on an agent that is attracted to a target in the absence of such coating.

18. A method as claimed in claim 17, wherein said substrate-agent conjugate comprises a carrier conjugate of a carrier polymer that bears said cytotoxic agent, and said carrier conjugate is condensed with a plurality of oligomers that are substrate for said enzyme, such that said carrier conjugate is released by action of said enzyme on said oligomers at the target site.

19. A method for targeting a cytotoxic agent to a target site, comprising the steps of:

(a) injecting a mammal parenterally with an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope on an enzyme, wherein binding to said epitope does not interfere with enzyme activity;

(b) subsequently injecting said mammal parenterally with an effective amount for enzyme activity of said enzyme, such that said bispecific antibody or antibody fragment binds said enzyme to form an antibody-enzyme conjugate in situ; and

(c) after a sufficient period of time for localization of said antibody-enzyme conjugate at the target site and for unbound antibody-enzyme conjugate to clear from the circulatory system of the mammal, further injecting said mammal parenterally with an effective amount for deposition at said site of a serum soluble substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising a cytotoxic agent that is relatively insoluble in serum in vivo, wherein the cytotoxic agent partitions out once the substrate-agent conjugate is acted upon by the enzyme component of the targeted

antibody-enzyme conjugate, so that the agent then accretes at the target site to a significantly greater extent than the substrate-agent conjugate would accrete in the absence of the enzyme;

wherein said enzyme is glucuronidase.

20. A sterile injectable preparation, for targeting a cytotoxic agent to a target site, comprising;

(a) a first sterile injectable solution containing an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope of an enzyme, wherein binding to said epitope does not interfere with enzyme activity, said antibody or antibody fragment being dissolved in a pharmaceutically acceptable sterile injection vehicle;

(b) a second sterile injectable solution containing an effective amount for enzyme activity at said target site of said enzyme, said enzyme being dissolved in a pharmaceutically acceptable sterile injection vehicle; and

(c) a third sterile injectable solution containing an effective amount, for deposition at said site, of a serum soluble substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising at least one cytotoxic agent that is relatively insoluble in serum in vivo, said substrate-agent conjugate comprising a substrate for said enzyme, wherein cleavage by the enzyme liberates serum soluble cytotoxic agent in situ, said substrate-agent conjugate being dissolved in a pharmaceutically acceptable sterile injection vehicle;

wherein said enzyme is glucuronidase.

21. A kit for targeting a cytotoxic agent to a target site, comprising;

(a) a first sterile container containing an effective amount for targeting of a bispecific antibody or antibody fragment having a first binding site specific for an antigen present at a target site and a second binding site specific for an epitope of an enzyme which does not interfere with enzyme activity;

(b) a second sterile container containing an effective amount for enzyme activity at said target site of said enzyme; and

(c) a third sterile container containing an effective amount for deposition at said site of a soluble substrate-agent conjugate which is capable of transformation by said enzyme to form a product comprising a cytotoxic agent, said substrate-agent conjugate comprising a substrate for said enzyme, wherein cleavage by the enzyme liberates soluble cytotoxic agent in situ,

wherein said enzyme is glucuronidase.

22. A method according to claim 1, wherein said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent.

23. A preparation according to claim 6, wherein said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent.

24. A kit according to claim 7, wherein said polymer substrate is a coating on the agent, which agent is one that is attracted to the target site in the absence of such coating, such that cleavage by the enzyme liberates the agent.

25. The method of claim 1, wherein said cytotoxic agent is at least one boron addend, drug, toxin, radioisotope, vasodilator, cytokine, radiosensitizer or photosensitizer.

26. The kit of claim 7, wherein said cytotoxic agent is at least one boron addend, drug, toxin, radioisotope, vasodilator, cytokine, radiosensitizer or photosensitizer.